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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/692,623	10/20/2000	Stephen M. Boyle	031786-046	2200

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EXAMINER
GRASER, JENNIFER E

ART UNIT	PAPER NUMBER
1645	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/692,623	Applicant(s) Boyle et al.
	Examiner Jennifer Graser	Art Unit 1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *Amendt. B 7/29/02*

2a)☒ This action is **FINAL.** 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-30* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideratio

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some* c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)

16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18)☐ Interview Summary (PTO-413) Paper No(s). _____

19)☐ Notice of Informal Patent Application (PTO-152)

20)☐ Other:

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Acknowledgment and entry of the Amendment submitted 7/29/02, Paper No. 9B is made. Claims 24-30 are currently pending and under examination. The former 102(b) rejection of Highlander et al has been overcome by Applicants' arguments.

Information Disclosure Statement

The information disclosure statement filed fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the non-patent literature documents listed have not been received by the Office. Parent file 09/091,521 could not be located at the time of this Office Action so it could not be determined if the documents were originally filed in the parent prosecution. Applicants noted that only some of the copies on the IDS were submitted in the parent case. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 24-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kontinen et al (WO 94/19471) and Highlander et al. (US 6,180,112).

Kontinen et al disclose a method and expression system for enhancing secretion of hyperproduced homologous and heterologous exoproteins in bacteria. It is specifically taught that methods for overexpressing secreted proteins were readily available in the prior art, such as increasing gene expression by using multicopy plasmids or enhancing the activity of the gene by modifying its regulatory elements, e.g., by using strong promoters or multiple promoters, resulting in dramatic increases in the synthesis of exoproteins. See page 4, lines 15-20. It is also taught that this method and system may be used with any gram-positive bacterium (page 8, lines 7-8). It also may be used with any desired exoprotein, including any Gram-positive bacterium, antigenic proteins of microbes and protozoa and capsule, outer membrane and fimbria proteins from any Gram-negative bacteria, including *M.tuberculosis, Vibrio cholerae.* It is also taught that any protein toxins or secreted proteins from bacteria, surface proteins of any microorganisms and antigen proteins or viruses may be overexpressed in the same manner as taught in the reference. Accordingly, this would include *Brucella* as recited in instant claim 27. It is taught that these proteins may be used as vaccines and pharmaceuticals. See page 8, line 11-page 10,

line 15. Additionally, the use of recombinant host cells which express an antigen that protects against disease, or the isolated antigen itself, were both widely used as vaccines in the prior art at the time the invention was made.

However, Kontinen et al. do not specifically disclose using the over-producing bacterial strains as vaccines, but rather teaches using the over-expressed products from the bacterial strains as the vaccines. Additionally, Kontinen et al. does not specifically recite the use of an attenuated or avirulent strain.

Highlander et al. discloses whole cell vaccine compositions comprising a recombinant, avirulent *Pasteurella haemolytica* organism which comprises a strong leukotoxin promoter which allows for homologous overexpression of said leukotoxin antigen. The *P.haemolytica* transcriptional activator is introduced on a multicopy plasmid (see bottom of column 42 and claim 8). It is specifically taught that since *P.haemolytica* leukotoxin genes are poorly expressed in *E.coli*, Pasteurella-specific transcriptional factors were used for this homologous, overexpression. Both methods and vaccine for the immunization, prophylaxis or treatment of vertebrates suffering from disease caused by *P.haemolytica* are specifically taught. The use of additional heterologous antigens are also taught. Highlander et al teach homologous over-expression of a desired antigen in an attenuated strain of Gram-negative bacteria and the use of this strain as a vaccine.

The prior art teaches that the use of multicopy plasmids and/or using strong promoters or multiple promoters was well known in the bacterial art for increasing the production of a

desirable protein product. The prior art also teaches that recombinant whole cell vaccines were well known. Kontinen et al teach that homologous over-expression was well known in the art. Highlander et al teach homologous over-expression of a desired antigen in an attenuated strain of Gram-negative bacteria and the use of this strain as a vaccine. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made that not only Gram-positive bacterium, but also attenuated or avirulent Gram-negative bacterium, as evidenced by Highlander et al., could be used to produce an homologous and/or homologous-heterologous expression system for the purpose of producing a vaccine. Highlander et al teaches that the expression system, itself, and not just the isolated expression products make effective vaccines. Further, official notice is taken that it was well known in the prior art that either the recombinant whole cell vaccine or the isolated product of a recombinant whole cell could be used as the major component in a vaccine composition.

Response to Applicants' Arguments:

Applicants argue that Kontinen does not disclose or suggest a method of immunization, prophylaxis or treatment wherin the attenuated or avirulent strain of an otherwise pathogenic micro-organism is administered. They further aruge that neither the over-expressed PrsA or the bacterium or the at least one exoprotein of interest are capable of stimulating protective immunity against the bacterium expressing them. They further argue that the secondary reference, Highlander et al, teaches over-expression of the leukotoxin polypeptide not the leukotoxin gene. These arguments have been fully and carefully considered but are not deemed

persuasive. First, it is noted that Applicants' argument regarding the references not teaching that their vaccines stimulate "protective immunity" is not commensurate in scope with the claimed invention which encompasses 'immunization'.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Kontinen et al is almost so close to the claimed invention that it could almost be a 102(b). Although the reference does suggest the use of vaccines and pharmaceuticals, it does not particularly exemplify the use of the recombinant bacterium as the vaccine, but instead suggests the use of its over-expressed products. As stated above, Kontinen teaches a method and expression system for enhancing secretion of hyperproduced homologous and heterologous exoproteins in bacteria. It is specifically taught that methods for overexpressing secreted proteins were readily available in the prior art, such as increasing gene expression by using multicopy plasmids or enhancing the activity of the gene by modifying its regulatory elements, e.g., by using strong promoters or multiple promoters, resulting in dramatic increases in the synthesis of exoproteins. See page 4, lines 15-20. It is taught that these products may be used as vaccines which by definition would confer protective immunity to a host.

Highlander et al. discloses whole cell vaccine compositions comprising a recombinant, avirulent *Pasteurella haemolytica* organism which comprises a strong leukotoxin promoter

which allows for homologous overexpression of said leukotoxin antigen. The *P.haemolytica* transcriptional activator is introduced on a multicopy plasmid (see bottom of column 42 and claim 8). It is specifically taught that since *P.haemolytica* leukotoxin genes are poorly expressed in *E.coli*, Pasteurella-specific transcriptional factors were used for this homologous, overexpression. Both methods and vaccine for the immunization, prophylaxis or treatment of vertebrates suffering from disease caused by *P.haemolytica* are specifically taught. The prior art teaches that the use of multicopy plasmids and/or using strong promoters or multiple promoters was well known in the bacterial art for increasing the production of a desirable protein product. The prior art also teaches that recombinant whole cell vaccines were well known. Kontinen et al teach that homologous over-expression was well known in the art. Highlander et al teach homologous over-expression of a desired antigen in an attenuated strain of Gram-negative bacteria and the use of this strain as a vaccine. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made that not only Gram-positive bacterium, but also attenuated or avirulent Gram-negative bacterium, as evidenced by Highlander et al., could be used to produce an homologous and/or homologous-heterologous expression system for the purpose of producing a vaccine. Highlander et al teaches that the expression system, itself, and not just the isolated expression products make effective vaccines.

3. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Note regarding Double patenting

4. The instant claims were restricted from the claims allowed in US Patent No. 6,149,920 during the prosecution of said parent application, formerly 09/091,521. The instant claims were also restricted from the claims pending in Divisional application 09/692,622 during the prosecution of parent application 09/091,521. Accordingly, a double patenting rejection cannot be made between the instant application and either of the related applications.

5. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is (703) 308-4242 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (703) 308-1742. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JENNIFER E. GRASER
PRIMARY EXAMINER
11/18/02